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Original Article

Clinical features and subtypes of restless legs syndrome in Chinese population: a study of 359 patients

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ABSTRACT

Background: The clinical spectrum of restless legs syndrome (RLS) has not been described in a Chinese population. We aim to evaluate the detailed clinical profile in a cohort of unselected RLS patients in China.

Methods: We enrolled RLS patients continuously according to the diagnostic criteria. Laboratory examinations were performed to exclude mimics and notable comorbidities.

Results: A total of 359 patients with RLS were enrolled. RLS symptoms were mostly symmetrical (65.2%), and purely unilateral RLS was not common (5.6%); however, unilateral dominant RLS was relatively more common. Only 1.1% of RLS patients reported no unpleasant sensations in the legs. The largest proportion of RLS patients described their uncomfortable sensation as indescribable (43.5%) and reported soreness (40.4%). In all, 8.9% of RLS patients described their abnormal sensation as painful, and 34.5% of RLS patients reported their symptoms fluctuated with seasonal trends. This population had a higher likelihood of an RLS family history. RLS patients with summer exacerbation had a younger age at RLS onset and longer disease duration ($p < 0.01$). Iron deficiency without anemia was common in Chinese RLS patients. Early-onset RLS patients were more likely to have a positive family history ($p < 0.01$), more summer worsening of symptoms ($p < 0.01$) and more severely disturbed peripheral iron status ($p < 0.01$) when compared to late-onset RLS patients.

Conclusion: The subjective description is somewhat different, with Chinese RLS patients reporting less pain and more soreness than patients from Western countries. Seasonal fluctuation and iron deficiency without anemia are frequently seen in Chinese RLS patients and predict some other features. Differentiating these various subtypes can facilitate optimal management.

1. Introduction

Restless legs syndrome (RLS) is a common sensory-motor neurological disorder characterized by an urge to move the legs (or other parts of the body), usually accompanied by uncomfortable sensations [1]. Despite detailed descriptions of clinical features of RLS in European and American countries, clinical features of RLS in Chinese population lack detailed data. The prevalence of RLS varies in different races and geographic areas [2]. Li et al., studied genetic factors of 116 primary RLS patients in a Chinese population. They confirmed that BTBD9 and MAP2K5/SKOR1were associated with RLS in Chinese primary RLS patients; however, they did not replicate an association of MEIS1, PTPRD, and TOX3/BC034767 in Chinese RLS patients. The authors postulated that ethnic heterogeneity might account for the distinction between Chinese and Western patients with RLS [3]. Besides possible genetic discrepancies between American and European RLS patients, Chinese RLS patients may also manifest different phenotypes, although the clinical spectrum of RLS in Chinese patients has not been studied in detail, except rarely and with a small sample size and focus on cognitive function and RLS [4]. We aimed to systematically investigate the clinical profile in a cohort of unselected RLS patients in China.

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2. Methods

2.1. Inclusion of patients

We recruited patients diagnosed with RLS from our Movement Disorders Clinic in Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, between Jun 2014 and July 2018. RLS was diagnosed according to the 2014 International Restless Legs Syndrome Study Group (RLSSG) diagnostic criteria [5]. Patients with cognitive impairment (Mini-Mental Status Examination [MMSE] score <24 [higher than middle school cultural level] or <20 [primary school level] or <17 [illiteracy]) were excluded from the study.

2.2. Standard protocol approvals and patient consent

The study was approved by the Shanghai General Hospital Institutional Review Board, and all patients and control subjects included in the study gave written consent.

2.3. Examination program

We interviewed subjects face-to-face and recorded demographic information, history, symptoms, medications, general neurologic and medical examinations, as well as MMSE for all recruited patients. Patients considered positive for RLS were examined again by another neurologist specialized in movement disorders; and were further assessed with a semi-structured questionnaire, which included age of RLS onset, RLS family history (familiality defined as "first-degree relatives"), type and topography of sensations, and whether RLS symptoms related to seasonal variation. RLS severity for one week prior to the interview was assessed using the International RLS Rating Scale (IRLSRS) [6]. Examination modalities such as vascular ultrasound, nerve conduction velocities, and electromyography were performed if necessary to exclude possible RLS mimics such as peripheral polyneuropathies, venous stasis, vascular claudication, and rheumatoid arthritis. Subjects with a medication history of neuroleptics or other medication that the authors considered might be related to RLS in the preceding three months were also excluded. We excluded individuals with notable comorbidities that were possibly associated with secondary RLS, such as chronic renal failure, pregnancy, Parkinson's disease, and ataxia. We also excluded RLS patients with significant iron deficiencies including anemia or nonanemic iron deficiency with known causes such as gastrointestinal hemorrhage, uterine fibroid hemorrhage, and malnutrition, since different pathologies of RLS may exist. Peripheral iron status was assessed by serum iron, ferritin, transferrin, and total iron-binding capacity (TIBC). Transferrin saturation (TSAT) was calculated as serum iron/TIBC × 100. Normal hemoglobin level was defined as ≥113 g/L in women and ≥131 g/L in men according to normal values in our hospital. Although serum ferritin is a sensitive marker for evaluating total body iron store, inflammatory status as well as other various conditions unrelated to iron status may influence its levels [7]. However, TSAT < 20% or serum ferritin 75 ≥ μg/L is suggested as iron deficiency [8]. Taken together, serum ferritin <75 μg/L or ferritin ≥75 μg/L but TSAT <20% may be indicative of low iron status [9,10].

2.4. Statistical analysis

Data were analyzed using SPSS 21.0 for Windows (IBM Corporation, Armonk, NY). All data are presented as means ± standard deviations. Since most of the variables were not normally distributed, the Mann–Whitney *U* test was used for single-variable comparisons between the two groups. The Kruskal–Wallis test was used for single-variable comparisons among multiple groups, and the post hoc Mann–Whitney test used when p was <0.05. Differences in proportions were analyzed by Pearson χ^2 or continuity correction when appropriate. Multiple comparisons were counteracted by using the Bonferroni correction, and the results were considered significant if the p value was <0.05/(23 comparisons) = 0.00217. Multivariate analysis of variance was used to compare RLS patients with and without iron deficiency to control for possible differences between the examined variables.

3. Results

A total of 474 patients agreed to participate in the study. Five of these individuals were excluded due to cognitive impairment, 98 were excluded due to comorbidities that possibly associated with secondary RLS (Table 1), and 12 were excluded due to atypical RLS during subsequent follow-up; therefore a total of 359 RLS patients were eligible for this study, including 119 male patients (33.1%) and 240 female patients (66.9%). The average age was 53.2 ± 13.8 years old. A total of 62.4% (224/359) RLS patients were without medication for RLS (185 were drug-naive, and 39 were drug-free for more than two weeks at interview). A total of 135 (37.6%) patients were taking medication for RLS at interview, among whom 76.3% were taking dopaminergics; others included gabapentin enacarbil, sleep medication, antidepressants/anxiolytics, and antiepileptics, with only two of the patients taking opioids (Table 2). Detailed demographic information and clinical features of patients with RLS are shown in Table 2.

3.1. Gender, age at onset, duration, and family history

Women experienced RLS almost twice as much as men in the whole group (66.9% vs 33.1%), and also more women had RLS (63.6%, 28/44) onset in childhood or adolescence (before age 20 years). This gender preponderance still existed in patients with RLS onset at age <35 years (66.7%, 108/162) and <45 years (69.4%, 161/232), respectively. The mean age of RLS onset was 38.0 ± 15.3 years, and the mean duration of RLS was 15.3 ± 12.0 years. In all, 64.6% of RLS patients developed their RLS symptoms before the age of 45 years. A total of 32.3% of RLS patients in this study reported a family history (first-degree relatives) of RLS (Table 2). When comparing RLS patients according to onset age of <45 years or ≥45 years, we found that the earlier-onset patients were younger at interview ($p < 0.0001$); had a shorter duration of RLS ($p < 0.0001$); had a more positive family history of RLS ($p < 0.00217$); and had lower iron status; including lower serum ferritin ($p < 0.0001$), higher serum transferrin ($p < 0.00217$), higher TIBC ($p < 0.0001$), a higher incidence of iron deficiency ($p < 0.0001$), and a worsening of RLS symptoms in the summer ($p < 0.00217$) (Table 3).

Table 1
Comorbidities possibly associated with secondary RLS (n = 98).

Comorbidity	Value
Iron-deficient anemia	36
Parkinson's disease	26
Chronic renal failure	10
Peripheral neuropathy	14
Diabetes	10
On medication such as neuroleptics	6
Stroke	3
Spinocerebellar ataxias	2
Brain trauma and epilepsy	1

RLS, restless legs syndrome.

Table 2
Demographic information and clinical features of RLS patients (N = 359).

Characteristic	Value
Age (yr)	53.2 ± 13.8
Gender, n (male, %)	119 (33.1%)
Smoking, n (%)	56 (15.6%)
Alcohol, n (%)	41 (11.4%)
BMI (kg/m^2)	23.8 ± 7.5
Ethnic Han, n (%)	357 (99.4%)
Shanghai local residents, n (%)	114 (31.8%)
Nonlocal residents, n (%)	245 (68.2%)
East China (non-Shanghai local)	172 (70.2%)
North China	14 (5.7%)
Central China	24 (9.8%)
South China	5 (2.0%)
Northwest China	8 (3.3%)
Northeast China	15 (6.1%)
Southwest China	7 (2.9%)
Without medication for RLS, n (%)	224 (62.4%)
Drug naive, n (%)	185 (51.5%)
Drug free, n (%)	39 (10.9%)
On medication for RLS, n (%)	135 (37.6%)
Dopaminergics, n (%)	103 (76.3%)
Gabapentin enacarbil, n (%)	29 (21.5%)
Others, n (%)	50 (37.0%)
Age at RLS onset (yr)	38.0 ± 15.3
Maximum	82
Minimum	3
Age at RLS onset < 45 yr, n (%)	232 (64.6%)
RLS family history, n (% positive)	116 (32.3%)
Duration of RLS (yr)	15.3 ± 12.0
≤5, n (%)	86 (24.0%)
<5–10, n (%)	92 (25.6%)
<10–20, n (%)	92 (25.6%)
>20, n (%)	89 (24.8%)
IRLSRS	23.8 ± 7.1
Mild (1–10)	20 (5.6%)
Moderate (11–20)	80 (22.3%)
Severe (21–30)	205 (57.1%)
Very severe (31–40)	54 (15.0%)
Chronic-persistent RLS, n (%)	329 (91.6%)
Intermittent RLS, n (%)	30 (8.4%)
Unilateral or unilateral dominant of RLS, n (%)	125 (34.8%)
Strictly unilateral RLS, n (%)	20 (5.6%)
Bilateral RLS with unilateral dominant, n (%)	105 (29.2%)
Extra body parts involvement beyond legs, n (%)	61 (17.0%)
Head and neck, n (%)	4 (1.1%)
Shoulder, n (%)	6 (1.7%)
Upper limbs, n (%)	42 (11.7%)
Back, n (%)	4 (1.1%)
Abdomen, n (%)	5 (1.4%)
Waist, n (%)	9 (2.5%)
Genital area, n (%)	3 (0.8%)
Locations affected in lower extremity	
Hip, n (%)	28 (7.8%)
Thigh, n (%)	160 (44.6%)
Calf, n (%)	278 (77.4%)
Knee, n (%)	119 (33.1%)
Popliteal fossa, n (%)	69 (19.2%)
Foot, n (%)	61 (17.0%)
Type of leg sensations	
Indescribable discomfort, n (%)	156 (43.5%)
Soreness, n (%)	145 (40.4%)
Crawling and formication, n (%)	114 (31.8%)
Biting, n (%)	41 (11.4%)
Painful sensory, n (%)	32 (8.9%)
Itching, n (%)	26 (7.2%)
Burning and heat, n (%)	15 (4.2%)
Tingling and prickling, n (%)	15 (4.2%)
Twitching and throbbing, n (%)	12 (3.3%)
Numbness, n (%)	10 (2.80%)
Tiredness and weakness, n (%)	10 (2.80%)
Stiffness and contraction, n (%)	6 (1.7%)
Coldness, n (%)	5 (1.4%)
Electrical, n (%)	4 (1.1%)
Without any leg sensations, n (%)	4 (1.1%)
Heaviness, n (%)	2 (0.56%)
RLS symptom fluctuation with seasonal trends, n (%)	124 (34.5%)
With worsening in summer, n (%)	55 (15.3%)
With worsening in winter, n(%)	35 (9.7%)
[a]Ferritin (μg/L)	148.1 ± 126.7
[a]Transferrin (g/L)	2.6 ± 0.5
[a]Iron (μmol/L)	17.5 ± 5.9
[a]TIBC (μmol/L)	57.9 ± 8.4
[a]TSAT	30.8% ± 10.5%
[a] TSAT < 20%, n (%)	36 (12.0%)

BMI, body mass index; IRLSRS, International Restless Legs Syndrome Rating Scale; RLS, restless legs syndrome; TIBC: total iron-binding capacity; TSTA, transferrin saturation.
[a] A total of 299 iRLS patients underwent the complete iron metabolic assessment.

3.2. RLS symptomatology

3.2.1. Clinical course

A majority of RLS patients had a chronic-persistent (329/359, 91.6%) rather than intermittent course (8.4%). It is worth noting that a majority of these patients with chronic-persistent RLS initially had intermittent RLS, which became chronic later, supporting the view of a slow progressive course of RLS [11]. The mean severity of RLS measured by the IRLSRS was 23.8 ± 7.1, and more than 70% were classified as having "severe" (57.1%, 205/359) or "very severe" (15.0%, 54/359) RLS (Table 2).

3.2.2. Anatomical distribution

We found that 34.8% (125/359) of RLS patients presented with unilateral or unilateral-dominant RLS symptoms, among whom 5.6% (20/359) had strictly unilateral RLS and 29.2% had bilateral RLS with unilateral dominance. Involvement beyond the legs was seen in 17.0% (61/359) of patients. Of note, about one-half (8.6%, 31/359) of these 61 RLS patients with extra-leg involvement were dopaminergic drug naive. Upper extremity (11.7% patients) was the most frequently involved body part beyond lower extremity. Other extra body parts involved were not common (Table 2). All RLS patients who had extra-leg involvement reported lower extremity discomfort. Except for two patients, all patients reported that the leg restlessness was more severe when compared to that of other body parts. Calves were the most frequently affected location of the lower extremity (77.4%, 278/359) (Table 2).

3.2.3. Abnormal sensory profiles

Various sensory descriptions were reported by RLS patients. "Indescribable discomfort" was the most frequently chosen description (43.5%), the next was "soreness" (40.4%), afterwards "crawling and formication" (31.8%), "biting" (11.4%), "itching" (7.2%), and other, relatively uncommon words (Table 2). A total of 8.9% (32/359) of RLS patients reported their abnormal sensation as being painful in this study. The nature of pain was described as prickling/stinging (n = 13), mild and vague aching (n = 13), dull pain (n = 2), throbbing/jumping (n = 2), tearing (n = 1), and knife-cutting (n = 1). RLS patients with painful sensations presented with higher scores on the IRLSRS ($p = 0.021$) and a greater proportion of severe/very severe RLS ($p = 0.042$) according to the IRLSRS, as well as higher levels of transferrin and TIBC ($p < 0.05$) when compared to RLS patients without painful sensations. However, the differences between RLS patients with or without painful sensations were not significant after Bonferroni correction ($p > 0.00217$) (Table 4). In addition to the given words, three patients using their own words to describe the discomfort: flesh-separation, emptiness of losing leg, and desire to urinate. Of note, four of the 359 patients (1.1%) reported that they only had the urge to move and did not feel any unpleasant sensation in the legs (Table 2).

Table 3
Comparison of EOR and LOR.

Characteristic	EOR (<45 yr) (n = 232)	LOR (≥45 yr) (n = 127)	*p*
Age (yr)	47.8 ± 13.3	63.2 ± 7.9	**Z = −10.621, *p* < 0.0001**
Gender, male, n (%)	71 (30.6%)	48 (37.8%)	$\chi^2 = 1.916$, $p = 0.166$
Age at RLS onset (yr)	28.8 ± 9.6	54.7 ± 7.7	**Z = −15.674, *p* < 0.0001**
Duration of RLS (yr)	18.9 ± 12.6	8.6 ± 6.9	**Z = −7.919, *p* < 0.0001**
RLS family history, n (% positive)	89 (38.4%)	27 (21.3%)	**$\chi^2 = 10.976$, $p = 0.001$**
IRLSRS	23.6 ± 7.1	24.1 ± 7.1	$Z = -0.733$, $p = 0.463$
Severe–very severe (21–40), n (%)	164 (70.7%)	95 (74.8%)	$\chi^2 = 0.691$, $p = 0.406$
Chronic–persistent RLS, n (%)	210 (90.5%)	119 (93.7%)	$\chi^2 = 1.086$, $p = 0.297$
Unilateral or unilateral dominant of RLS, n (%)	76 (32.8%)	49 (38.6%)	$\chi^2 = 1.227$, $p = 0.268$
Strictly unilateral RLS, n (%)	12 (5.2%)	8 (6.3%)	$\chi^2 = 0.198$, $p = 0.656$
Extra body parts involvement beyond legs, n (%)	37 (15.9%)	24 (18.9%)	$\chi^2 = 0.506$, $p = 0.477$
With seasonal fluctuation, n (%)	91 (39.2%)	33 (26.0%)	$\chi^2 = 6.363$, $p = 0.012$
With worsening in summer	46 (19.8%)	9 (7.1%)	**$\chi^2 = 10.27$, $p = 0.001$**
With worsening in winter	21 (9.1%)	14 (11.0%)	$\chi^2 = 0.363$, $p = 0.547$
[a]Ferritin (μg/L)	113.3 ± 99.7	186.7 ± 126.8	**Z = −4.948, *p* < 0.0001**
[a]Transferrin (g/L)	2.7 ± 0.5	2.5 ± 0.4	**Z = −3.279, *p* = 0.001**
[a]Iron (μmol/L)	17.8 ± 6.4	16.9 ± 4.8	$Z = -1.270$, $p = 0.204$
[a]TIBC (μmol/L)	59.3 ± 8.6	55.3 ± 7.1	**Z = −4.025, *p* < 0.0001**
[a]TSTA	30.8% ± 11.5%	30.9% ± 8.7%	$Z = -0.448$, $p = 0.654$
[a]TSAT < 20%, n (%)	26 (13.8%)	10 (9.0%)	$\chi^2 = 1.532$, $p = 0.216$
[a]Iron deficiency, n (%)	91 (48.7%)	29 (25.9%)	**$\chi^2 = 15.116$, $p < 0.0001$**

EOR, early-onset restless legs syndrome; IRLSRS, International Restless Legs Syndrome Rating Scale; LOR, late-onset restless legs syndrome; RLS, restless legs syndrome; TIBC, total iron-binding capacity; TSTA, transferrin saturation.
Mann–Whitney test for comparison of continuous variables, Pearson χ^2 or Fisher exact test for categorical variables.
P values less than 0.05 (before the Bonferroni correction) were emphasized in bold.
[a] A total of 299 RLS patients underwent the complete iron metabolic assessment.

3.2.4. Seasonal fluctuation

Approximately one-third (34.5%, 124/359) of RLS patients reported that their RLS symptoms fluctuated with seasonal trends or weather variation, among whom 55/359 (15.3%) had worsening symptoms in summer, 35/359 (9.7%) in winter, 13/359 (3.6%) during seasonal changes, and 21/359 (5.8%) in wet weather. Another 22 patients did not notice or could not remember whether their RLS symptoms were related with seasonal fluctuation.

We compared features of summer-aggravated RLS, winter-aggravated RLS, and RLS without seasonal fluctuation. We found that summer-aggravated RLS patients had an earlier age of onset ($p < 0.00217$) and longer duration ($p < 0.00217$) than either winter-aggravated RLS or RLS without seasonal fluctuation (Table 5). Summer-aggravated RLS patients also had a trend of a greater proportion of "very severe" RLS ($p = 0.028$) and higher TIBC values ($p = 0.02$) than patients with RLS without seasonal trends; however, there was no significance after Bonferroni correction ($p > 0.00217$). Both summer- and winter-aggravated RLS patients had a trend of more RLS family history compared to RLS patients without seasonal variation, although, again, without significance after Bonferroni correction ($p = 0.007 > 0.00217$). No differences were found regarding gender or age at interview between summer- and winter-aggravated RLS and RLS without seasonal fluctuation (Table 5).

Table 4
Features of RLS patients with or without painful sensation.

Characteristic	With painful sensation (n = 32)	Without painful sensation (n = 327)	*p*
Age (yr)	57.0 ± 16.2	52.9 ± 13.5	$Z = -1.644$, $p = 0.1$
Gender, male, n (%)	10 (31.1%)	109 (33.3%)	$\chi^2 = 0.057$, $p = 0.811$
Age at RLS onset (yr)	42.8 ± 15.6	37.5 ± 15.2	$Z = -1.534$, $p = 0.125$
Duration of RLS (yr)	14.3 ± 13.3	15.4 ± 11.9	$Z = -0.907$, $p = 0.364$
RLS family history, n (% positive)	7 (21.9%)	109 (33.3%)	$\chi^2 = 1.75$, $p = 0.186$
IRLSRS	26.1 ± 6.8	23.5 ± 7.1	**Z = −2.313, *p* = 0.021**
Severe–very severe (21–40), n (%)	28 (87.5%)	231 (70.6%)	**$\chi^2 = 4.122$, $p = 0.042$**
Chronic–persistent RLS, n (%)	32 (100%)	297 (90.8%)	$\chi^2 = 2.118$, $p = 0.146$
Unilateral or unilateral dominant of RLS, n (%)	11 (34.4%)	114 (34.9%)	$\chi^2 = 0.003$, $p = 0.956$
Strictly unilateral RLS, n (%)	2 (6.3%)	18 (5.5%)	$\chi^2 = 0.000$, $p = 1.000$
Extra body parts involvement beyond legs, n (%)	6 (18.8%)	55 (16.8%)	$\chi^2 = 0.077$, $p = 0.781$
With seasonal fluctuation, n (%)	15 (46.9%)	109 (33.3%)	$\chi^2 = 2.364$, $p = 0.124$
With worsening in summer	7 (21.9%)	48 (14.7%)	$\chi^2 = 0.675$, $p = 0.411$
With worsening in winter	4 (12.5%)	31 (9.5%)	$\chi^2 = 0.056$, $p = 0.812$
[a]Ferritin (μg/L)	124.1 ± 121.8	150.2 ± 128.3	$Z = -1.147$, $p = 0.251$
[a]Transferrin (g/L)	2.8 ± 0.4	2.6 ± 0.5	**Z = −2.419, *p* = 0.016**
[a]Iron (μmol/L)	17.8 ± 7.5	17.4 ± 5.7	$Z = -0.017$, $p = 0.986$
[a]TIBC (μmol/L)	61.4 ± 8.1	57.3 ± 8.2	**Z = −2.203, *p* = 0.028**
[a]TSTA	29.9% ± 13.4%	30.9% ± 10.3%	$Z = -0.812$, $p = 0.417$
[a]TSAT < 20%, n (%)	5/23 (21.7%)	30/276 (10.9%)	$\chi^2 = 1.489$, $p = 0.222$
[a]Iron deficiency, n (%)	10/23 (43.5%)	110/276 (39.9%)	$\chi^2 = 0.116$, $p = 0.733$

IRLSRS, International Restless Legs Syndrome Rating Scale; RLS, restless legs syndrome; TIBC: total iron-binding capacity; TSTA: transferrin saturation.
Mann–Whitney test for comparison of continuous variables, Pearson χ^2 or Fisher exact test for categorical variables.
P values less than 0.05 (before the Bonferroni correction) were emphasized in bold.
[a] A total of 299 RLS patients underwent the complete iron metabolic assessment.

Table 5
Comparison of RLS patients with or without seasonal fluctuation.

Characteristic	Summer exacerbation (n = 55)	Winter exacerbation (n = 35)	Without seasonal fluctuation (n = 213)	*p*
Age (yr)	51.6 ± 11.9	51.0 ± 14.6	53.5 ± 14.2	H = 1.798, $p = 0.407$
Gender, male, n (%)	14 (25.5%)	9 (25.7%)	73 (34.3%)	$\chi^2 = 2.222$, $\mathbf{p = 0.329}$
Age at RLS onset (yr)	31.1 ± 14.0	38.2 ± 15.0	39.6 ± 15.0	**H = 12.003, $p = 0.002$**[f, c]
Duration of RLS (yr)	20.5 ± 12.5	12.8 ± 10.5	13.9 ± 11.7	**H = 14.755, $p = 0.001$**[g,c]
RLS family history, n (% positive)	23 (41.8%)	18 (51.4%)	59 (27.7%)	$\chi^2 =$ **10.016, $p = 0.007$**[b,e]
IRLSRS	25.3 ± 6.2	22.9 ± 6.4	23.7 ± 7.2	H = 4.427, $p = 0.109$
Mild (1–10)	0 (0%)	3 (8.6%)	14 (6.6%)	$\chi^2 = 4.899$, $p = 0.08$
Moderate (11–20)	15 (27.3%)	4 (11.4%)	54 (25.4%)	$\chi^2 = 3.558$, $p = 0.169$
Severe (21–30)	26 (47.3%)	26 (74.3%)	115 (54.0%)	$\chi^2 =$ **6.676, $p = 0.036$**[f, d]
Very severe (31–40)	14 (25.5%)	2 (5.7%)	30 (14.1%)	$\chi^2 =$ **7.143, $p = 0.028$**[f,b]
Chronic-persistent RLS, n (%)	52 (94.5%)	30 (85.7%)	195 (91.5%)	$\chi^2 = 2.142$, $p = 0.343$
Unilateral or unilateral dominant of RLS, n (%)	19 (34.5%)	13 (37.1%)	73 (34.3%)	$\chi^2 = 0.11$, $p = 0.947$
Strictly unilateral RLS, n (%)	3 (5.5%)	4 (11.4%)	10 (4.7%)	$\chi^2 = 2.577$, $p = 0.276$
Extra body parts involvement beyond legs, n (%)	12 (21.8%)	6 (17.1%)	31 (14.6%)	$\chi^2 = 1.729$, $p = 0.421$
[h]Northern part of China, n (%)	13 (23.6%)	5 (14.3%)	36 (16.9%)	$\chi^2 = 1.692$, $p = 0.429$
[a]Ferritin (μg/L)	126.5 ± 123.0	131.3 ± 107.5	151.1 ± 130.0	H = 2.333, $p = 0.311$
[a]Transferrin (g/L)	2.7 ± 0.5	2.7 ± 0.4	2.6 ± 0.4	H = 4.776, $p = 0.092$
[a]Iron (μmol/L)	17.6 ± 6.5	18.8 ± 6.3	17.1 ± 5.5	H = 0.757, $p = 0.685$
[a]TIBC (μmol/L)	60.4 ± 9.2	58.9 ± 8.0	57.2 ± 7.6	**H = 7.78, $p = 0.02$**[c]
[a]TSTA	29.7% ± 11.0%	32.4% ± 12.7%	30.6% ± 10.1%	H = 0.355, $p = 0.837$
[a]TSAT < 20%, n (%)	6 (12.5%)	3 (10.7%)	22 (12.3%)	$\chi^2 = 0.075$, $p = 1.000$
[a]Iron deficiency, n (%)	23 (47.9%)	12 (42.9%)	71 (39.7%)	$\chi^2 = 1.083$, $p = 0.582$

IRLSRS, International Restless Legs Syndrome Rating Scale; RLS, restless legs syndrome; TIBC, total iron-binding capacity; TSTA, transferrin saturation.
Kruskal–Wallis test for comparison of continuous variables, post hoc Mann–Whitney test when $p < 0.05$, Pearson χ^2 or Fisher exact test for categorical variables.
P values less than 0.05 (before the Bonferroni correction) were emphasized in bold.
[a] A total of 299 RLS patients underwent the complete iron metabolic assessment.
[b] "RLS aggravated in summer" vs "RLS without seasonal fluctuation" at $p < 0.05$.
[c] "RLS aggravated in summer" vs "RLS without seasonal fluctuation" at $p < 0.01$.
[d] "RLS aggravated in winter" vs "RLS without seasonal fluctuation" at $p < 0.05$.
[e] "RLS aggravated in winter" vs "RLS without seasonal fluctuation" at $p < 0.01$.
[f] "RLS aggravated in summer" vs "RLS aggravated in winter" at $p < 0.05$.
[g] "RLS aggravated in summer" vs "RLS aggravated in winter" at $p < 0.01$.
[h] Northern and southern part of China is divided by the geographical Qinling Mountains–Huaihe River line.

3.3. Iron status in RLS

In sum, 299 patients of the total 359 nonanemic RLS patients underwent evaluation of iron parameters including serum iron, ferritin, transferrin, and TIBC. Low iron status, as determined by serum ferritin <75 μg/L or serum ferritin ≥75 μg/L but TSAT <20% with normal hemoglobin level was found in 40.1% (120/299) of RLS patients of this group. It is worth noting that 10.8% (13/120) among these nonanemic iron-deficiency patients had a decreased TSAT <20%; however, their ferritin levels were within normal range.

More female RLS patients had iron deficiency compared than those without iron deficiency (91.7% vs 52.0%, $\chi^2 = 51.972$, $p < 0.001$). Considering female gender as a confounding factor to iron deficiency, we compared RLS with and without iron deficiency by multivariate analysis of variance with gender as a covariance. We found that patients with low iron status had a younger age both at interview ($p < 0.001$) and at RLS onset ($p < 0.001$), and more had an RLS onset before age 45 years ($p = 0.001$) (Table 6). Female gender was significantly associated with age at interview ($p = 0.002$), serum levels of ferritin ($p < 0.001$) and iron ($p < 0.001$), as well as TSTA values ($p = 0.001$) (Table 6).

4. Discussion

4.1. RLS profile in Chinese patients

We found that both onset age of <35 years and >35 years in female patients was almost twice that of male patients. Most European or US studies [5,12,13], and also studies from Korea [14] and Japan [15] reported female gender is a risk factors for RLS. Previous studies on Caucasian/white individuals reported that gender dominance correlated with different onset ages. Some studies showed that a gender preponderance existed only in adults whose RLS onset age was >35 years [16], whereas for adults <35 years of age or for children, there was little or no gender difference [17,18]. Other studies found higher a female prevalence only in parous women [19,20]. Alternately, several studies demonstrated a similar gender preponderance for women across all onset ages [13,21]. Limited onset age-related gender differences in RLS have been reported in an Asian population. We found a similar gender difference irrespective of onset age in our study, which supports the viewpoint that genetic factors contribute to a higher rate of RLS in women [22]. Another explanation for the gender distribution discrepancy of RLS is different perceptions between male and female individuals [23].

RLS symptoms beyond the legs are not uncommon. We found that 17% of RLS patients had extra-leg involvement, most commonly that of the upper limbs (Table 2). Michaud et al., reported that 48.7% of their RLS patients from Canada had arm restlessness [24]. Recently, Yeh et al., studied 122 RLS patients in the United States and found that 35.25% had upper limb involvement; however, they also included patients with RLS concurrent with other leg conditions [25]. Koo et al., from Korea, found relatively lower incidence (27.5%) of extra-leg symptoms [26]. We also found a relatively lower incidence of extra body restless beyond the legs. This may be due to carefully excluding secondary factors, relatively less confounding from dopaminergic drug therapy-induced augmentation (since nearly two-thirds [62.4%] of RLS patients were free of dopaminergics), or ethnic factors.

RLS usually affects the legs bilaterally and symmetrically. In an earlier study, Ondo et al., studied a series of 54 RLS cases in the United States; the authors reported that most RLS patients presented with bilateral symptoms either alternating with or concurrently in the limbs, and that only 12.3% of the patients had unilateral predominance symptom without strictly unilateral RLS

Table 6
Comparison of RLS patients with or without low iron status.

Characteristic	With low iron status (n = 120)	Without low iron status (n = 179)	Covariate (gender)		Group	
			F	*p*	*F*	*p*
Age (yr)	48.4 ± 14.3	57.0 ± 11.2	**9.612**	**0.002**	**33.961**	**<0.0001**
Age at RLS onset (yr)	34.1 ± 14.9	42.1 ± 14.5	0.229	0.633	**14.364**	**<0.0001**
Age at RLS onset before 45, n (%)	91 (75.8%)	96 (53.6%)	0.86	0.355	**12.216**	**0.001**
Duration of RLS (yr)	14.5 ± 11.4	15.0 ± 11.6	7.331	0.07	2.120	0.147
RLS family history, n (% positive)	38 (31.7%)	60 (33.5%)	0.762	0.383	0.893	0.345
IRLSRS	23.9 ± 7.5	24.0 ± 6.5	2.58	0.109	0.424	0.516
Severe–very severe (21–40), n (%)	87 (72.5%)	131 (73.2%)	2.029	0.155	0.026	0.871
Chronic-persistent RLS (%)	109 (90.8%)	167 (93.3%)	0.886	0.347	0.852	0.357
Unilateral or unilateral dominant of RLS (n,%)	44 (36.7%)	63 (35.2%)	3.820	0.052	0.315	0.575
Strictly unilateral RLS, n (%)	8 (6.7%)	8 (4.5%)	0.307	0.580	1.188	0.277
Extra body parts involvement beyond legs, n (%)	23 (19.2%)	29 (16.2%)	0.803	0.371	0.94	0.333
With seasonal fluctuation, n (%)	45 (37.5%)	58 (32.4%)	0.104	0.747	0.08	0.778
[a]Ferritin (μg/L)	48.1 ± 37.7	212.9 ± 121.8	**37.423**	**<0.0001**	**118.867**	**<0.0001**
[a]Transferrin (g/L)	2.8 ± 0.6	2.5 ± 0.3	0.062	0.804	**24.468**	**<0.0001**
[a]Iron (μmol/L)	15.8 ± 5.8	18.7 ± 5.5	**13.761**	**<0.0001**	**4.628**	**0.032**
[a]TIBC (μmol/L)	61.2 ± 9.4	55.5 ± 6.4	0.034	0.854	**27.335**	**<0.0001**
[a]TSTA	26.5% ± 10.9%	33.7% ± 9.2%	**11.665**	**0.001**	**14.986**	**<0.0001**
[a]TSAT < 20%, n (%)	35 (29.2%)	0 (0%)	0.666	0.415	**41.983**	**<0.0001**

IRLSRS, International Restless Legs Syndrome Rating Scale; RLS, restless legs syndrome; TIBC, total iron-binding capacity; TSTA, transferrin saturation.
Multivariate analysis of variance with gender as a covariance.
P values less than 0.05 (before the Bonferroni correction) were emphasized in bold.
[a] A total of 299 RLS patients underwent the complete iron metabolic assessment.

[27]. Recently, Shukla et al., from India, included both primary and secondary RLS, and demonstrated that unilateral RLS was not rare and was associated more with secondary factors [28]. Koo et al., from Korea, excluded notable comorbidities associated with secondary RLS, and found that 24% of patients presented with an asymmetric distribution, of whom 14% had strictly unilateral RLS symptoms [26]. Karroum et al., excluded secondary RLS and reported a 34% predominantly unilaterality in French RLS patients, among whom six of the 44 patients (13.6%) described RLS sensation as "always unilateral" [29]. We found an even lower incidence (5.6%) of strictly unilateral RLS. Taken together, we believe that in both Caucasian/white individuals and Asians, unilateral predominance is relatively common, whereas strict unilaterality is not common but does exist in patients with RLS. Secondary causes should be carefully excluded in purely unilateral cases.

In regard to sensory profiles, we found that a large proportion in our patients characterized their unpleasant sensation as indescribable (43.5%) and as soreness (40.4%), which were the most frequently chosen words to describe the type of abnormal sensation. Other sensations include formication, itching, prickling, biting, crawling, electrical, tingling, burning, numbness, and pain. Notably, we found in some cases that there were different types of abnormal sensations in different parts of the body, and some patients reported the type of sensation changing during the disease course.

RLS is reported to have painful characteristics, and pain is a frequent complaint of RLS patients [30]. The effectiveness of analgesics in treating RLS suggests that the mechanisms underlying sensory processing in primary RLS and the pain modulation pathways overlap [31], which may involve the spinal neural network and the medial pain system [32]. Most studies in Caucasian/white individuals showed more than one-half of RLS patients reported painful sensations [30,33–35]. Karroum et al., found a 61% prevalence of painful RLS in a French clinical series of 56 primary RLS patients [33]. Another study in Europe included 55 unselected RLS (including secondary RLS) patients; the authors found that 56% of the patients reported that their sensory disturbances were painful, and that painful sensations were more frequent in elderly patients and more commonly associated with disorders of the peripheral nervous system [35]. After excluding RLS mimics and secondary RLS, we found a lower proportion of painful RLS (8.9%, 32/359). Painful RLS was associated with more severe RLS compared to nonpainful RLS in our study (Table 4), consistent with the report of Karroum et al., who considered painful RLS to be a severe, "burning" subtype of RLS [36]. However, we did not find painful RLS in our cohort more often described as "burning," and this small subset of patients with unpleasant sensations being painful described the nature of pain as prickling and/or mild and vague aching; sharp pain was unusual in RLS patients in our study, which, however, we had observed mostly in RLS patients secondary to neuropathy (unpublished data). We consider that the lesser painful sensation in this case may be due to ethnic factors or language issues, as well as excluding possible secondary factors associated with RLS. RLS patients comorbid with neuropathy and/or myelopathy are more frequently susceptible to painful dysesthesia phenotype [32–34]. Quantitative sensory testing measurements have detected nociceptive sensory symptom impairments such as mechanical hyperalgesia in primary RLS patients [37–39]. In comparison with primary RLS patients, those with RLS secondary to neuropathies (including both large- and small-fiber neuropathies) more frequently complain of painful dysesthesia symptoms such as burning and shooting pains in the feet [38,40,41]. Furthermore, pain is an integrated experience not only in terms of neurological/physical status, but also in terms of emotional and behavioral responses. The reported prevalence of painful RLS sensation was relatively lower (17%) in an African study, although the sample size was small, with only 41 RLS patients [42]. Ethnic variability in pain perception as well as cultural variation may partly explain the less painful RLS reported in our group [43].

Leg motor restlessness and paresthesia are key features in RLS. RLS is diagnosed by an urge to move the limbs, and paresthesia, although generally accompanied, is not necessary for diagnosis [5]. We found that only 1.1% of subjects reported no unpleasant/uncomfortable leg sensations. One German study showed that eight of 40 RLS patients had no sensory symptoms at all, whereas others had various sensory symptoms [37]. Our results confirm the view that RLS without any unpleasant sensations in the legs (as well as other body parts) is also uncommon in Chinese patients. Ondo et al., described two patients with spinal pathology who lacked any urge to move, and thus were not diagnosed with RLS, but had persistent involuntary leg kicks that dramatically responded to dopamine agonists. They proposed this as "pure motor RLS" [44]. Whether RLS without any sensation shares any similar mechanism with the so-called pure motor RLS needs further investigation.

Seasonal variation of RLS has not been systematically investigated in either Caucasian/white or Asian individuals. Previous studies of cases [45,46]and Internet search query data [47] yielded a seasonality of RLS symptomatology with a peak in summer. However, another study reported the opposite, namely, that RLS symptoms were exacerbated in winter [48]. We previously found that seasonal fluctuation was common in RLS patients in a smaller study [49]. In this study, we confirmed that RLS symptoms frequently (34.5%, 124/359) fluctuated with seasonal trends or weather variation. There were different patterns of seasonal variation, with more patients reporting their symptoms as aggravated in summer (15.3%, 55/359) more than in winter (9.7%, 35/359) (Tables 2 and 5). In addition, some patients (5.8%, 21/359) did not show a pattern of summer or winter peak of RLS symptoms but instead reported their symptoms as aggravated during seasonal changes. Others (5.8%, 21/359) reported exacerbation in wet weather. A detailed history is necessary for deciding upon subsequent therapeutic strategies. The underlying mechanism of seasonal variation of RLS symptomatology is unclear. There is a circadian rhythm of melatonin secretion related to latitude, and melatonin has a potential effect on aggravating or inducing RLS symptoms, given its mutual inhibitory effects with dopamine [50,51]. Since the Qinling Mountains–Huaihe River line is a geographical boundary of latitude, climate, and temperature between the northern and southern part of China, we compared seasonal variation of RLS in north and southern China divided by this boundary, and we did not find a significant difference (Table 5). Brain iron deficiency is a critical factor in the pathogenesis in RLS [52,53]. Serum ferritin is an indicator of tissue iron stores, and its level is found to be inversely related to RLS severity [54,55]. There is evidence of fluctuation of peripheral iron parameters in serum around the year, with an ebb of iron stores in the late spring and summer in healthy people [56]. We found that a higher TIBC value in summer was associated with aggravated RLS than with RLS without seasonal trends ($p = 0.02$); yet, this was not significant after Bonferroni correction (Table 5), indicating that potential iron deficiency aggravated RLS with a seasonal pattern. RLS patients with borderline iron stores may be in lower iron status in summer, and are more susceptible to or present with more severe RLS symptoms in this season [47]. Longitudinal evaluation of peripheral iron parameters may be helpful to illuminate the hypothesis of seasonal variation of iron stores contributing to seasonal trends in RLS.

4.2. Nonanemic iron deficiency

Iron deficiency is common in RLS, and iron-deficient anemia is a recognized comorbidity associated with secondary RLS [57]. The association of RLS with nonanemic iron deficiency, which is often more insidious, is largely unknown. Iron dysregulation is known to play an important role in the pathogenesis of RLS because pathology studies show reduced brain iron in RLS [52], and iron-deficiency conditions, such as anemia and pregnancy, are associated with a higher prevalence of RLS [53]. Iron deficiency also relates to the dopamine system based on a series of animal and human studies [58]. Multiple genetic risk factors are associated with RLS [59]. MEIS1 and BTBD9, two genes associated both directly and indirectly with RLS, mediate iron and dopamine availability [59]. MEIS1 is modulated by intraneuronal iron status [60] and may also be involved in the modulation of BTBD9 expression and the subsequent downstream effect on iron [60].

Several randomized clinical trials set ferritin levels below 75 μg/L as indicating “low iron status,” which responded to oral or intravenous iron supplementary therapy [9,10,61,62]. It is worth noting that Trenkwalder et al., reported “iron-deficient nonanemia” RLS patients who also benefited from intravenous ferric carboxymaltose therapy [9].

Although there is consensus that iron deficiency is common in RLS patients, there has been little evidence on the prevalence of iron deficiency in Chinese RLS patients without anemia, and whether these RLS patients with iron deficiency represent a specific subgroup of RLS is not clear. Although we excluded RLS with iron-deficiency anemia or nonanemic iron deficiency with notable causes, low iron status is common (40.1%) in this group of non-anemia RLS patients. We found that female gender, as well as younger age both at RLS onset and at interview, were associated with iron deficiency (Table 6). Studies in Caucasian/white individuals do not show a strong inverse correlation in younger patients as opposed to older patients [63], although low CSF ferritin levels do correlate with RLS more in younger patients compared with older patients [64].

4.3. Different clinical profiles of early- and late-onset RLS

Early-onset RLS (EOR) is considered to represent a population different from late-onset RLS (LOR) [65–68]. Most studies set the cut-off onset age of EOR at age 45 years [11,65–68]. In this study, we found that the EOR group had more positive RLS family history, longer duration of RLS, more severely disturbed peripheral iron parameters (serum ferritin, transferrin, and TIBC), more iron deficiency, and more worsening of RLS symptoms in summer when compared to the LOR group (Table 3). Our study confirmed the dichotomy between EOR and LOR in Chinese patients. A younger age of RLS onset raises the possibility of a familial form, iron deficiency, and seasonal fluctuation, which may influence subsequent therapeutic strategies. On the other hand, older age of onset warrants attention for treatable secondary factors causing RLS [28].

4.4. Study limitations

Our study had some limitations. First, due to the cross-sectional nature of this study, we could not explore a longitudinal picture of RLS features. Sensory profile, location discomfort, seasonal variation, or other RLS symptomatology may evolve over time. Furthermore, there may be a recall bias. Second, more than one-third of RLS patients in this study were on dopaminergic drug and/or gabapentin enacarbil therapy, which may influence clinical features. Third, this was a single movement disorder center-based study. Nearly one-third of the patients were Shanghai local residents, and a majority of patients were from East China. Considering the vast territory of China and the possibility of various environmental factors, there may be a selection bias.

However, our study does have some advantages. We studied in detail the clinical spectrum of RLS in a relatively large group in Chinese patients in our Parkinson's Disease and Movement Disorders Center, and excluded notable secondary RLS or RLS mimics. We followed up each patient face-to-face or by telephone, and we carefully excluded those patients with atypical RLS during follow-up. We also explored EOR and LOR features, seasonal fluctuation, as well as clinical characteristics of nonanemic iron deficiency for the first time in China.

5. Conclusion

Laterality and location of RLS symptoms are mostly similar in Chinese RLS patients compared with RLS patients from Western countries. There is a somewhat different sensory pattern of less “pain” description and more “soreness” reported in Chinese RLS patients compared to their Caucasian/white counterparts. The majority of RLS patients cannot clearly report the type of sensation

and characterize it as “indescribable discomfort,” and RLS without any unpleasant sensations in the legs is rare. Seasonal fluctuation is frequently seen in RLS patients, with summer exacerbation correlating with younger age at onset and longer duration of RLS. Iron deficiency without anemia is common in this cohort of patients, especially in women and patients with younger age both at RLS onset and at interview, thus warranting attention for iron supplementary therapy. Early-onset RLS patients are more likely to have a positive family history, iron deficiency, and low peripheral iron status, as well as a trend of fluctuation of RLS symptoms with seasonal fluctuation and especially aggravation in summer, when compared to late-onset RLS patients. Differentiating these various subtypes can facilitate appropriate treatment.

Conflict of interest

We declare no conflict of interest.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.053.

References

[1] Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: treatment of restless legs syndrome in adults: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology 2016;87:2585–93.
[2] Tan EK, Seah A, See SJ, et al. Restless legs syndrome in an Asian population: a study in Singapore. Move Disord 2001;16:577–9.
[3] Li G, Tang H, Wang C, et al. Association of BTBD9 and MAP2K5/SKOR1 with restless legs syndrome in Chinese population. Sleep 2017;40.
[4] Li G, Tang H, Chen J, et al. Executive and visuospatial dysfunction in patients with primary restless legs syndrome/Willis-Ekbom disease: study of a Chinese population. J Clin Sleep Med 2018;14:785–90.
[5] Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (RLSSG) consensus criteria—history, rationale, description, and significance. Sleep Med 2014;15:860–73.
[6] Walters AS, LeBrocq C, Dhar A, et al. Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
[7] Khan A, Khan WM, Ayub M, et al. Ferritin is a marker of inflammation rather than iron deficiency in overweight and obese people. J Obes 2016;2016:1937320.
[8] Mackie S, Winkelman JW. Normal ferritin in a patient with iron deficiency and RLS. J Clin Sleep Med 2013;9:511–3.
[9] Trenkwalder C, Winkelmann J, Oertel W, et al. Ferric carboxymaltose in patients with restless legs syndrome and nonanemic iron deficiency: a randomized trial. Move Disord 2017;32:1478–82.
[10] Allen RP, Picchietti DL, Auerbach M, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med 2018;41:27–44.
[11] Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med 2000;1:11–9.
[12] Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. Neurology 2000;54:1064–8.
[13] Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev 2012;16:283–95.
[14] Cho YW, Shin WC, Yun CH, et al. Epidemiology of restless legs syndrome in Korean adults. Sleep 2008;31:219–23.
[15] Mizuno S, Miyaoka T, Inagaki T, et al. Prevalence of restless legs syndrome in non-institutionalized Japanese elderly. Psychiatry Clin Neurosci 2005;59:461–5.
[16] Xiong L, Montplaisir J, Desautels A, et al. Family study of restless legs syndrome in Quebec, Canada: clinical characterization of 671 familial cases. Arch Neurol 2010;67:617–22.
[17] Picchietti D, Allen RP, Walters AS, et al. Restless legs syndrome: prevalence and impact in children and adolescents – the Peds REST study. Pediatrics 2007;120:253–66.
[18] Yilmaz K, Kilincaslan A, Aydin N, et al. Prevalence and correlates of restless legs syndrome in adolescents. Dev Med Child Neurol 2011;53:40–7.
[19] Berger K, Luedemann J, Trenkwalder C, et al. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004;164:196–202.
[20] Pantaleo NP, Hening WA, Allen RP, et al. Pregnancy accounts for most of the gender difference in prevalence of familial RLS. Sleep Med 2010;11:310–3.
[21] Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–92.
[22] Bentley AJ, Rosman KD, Mitchell D. Gender differences in the presentation of subjects with restless legs syndrome. Sleep Med 2006;7:37–41.
[23] Garcia-Borreguero D, Egatz R, Winkelmann J, et al. Epidemiology of restless legs syndrome: the current status. Sleep Med Rev 2006;10:153–67.
[24] Michaud M, Chabli A, Lavigne G, et al. Arm restlessness in patients with restless legs syndrome. Move Disord 2000;15:289–93.
[25] Yeh P, Ondo WG, Picchietti DL, et al. Depth and distribution of symptoms in restless legs syndrome/Willis-Ekbom disease. J Clin Sleep Med 2016;12:1669–80.
[26] Koo YS, Lee GT, Lee SY, et al. Topography of sensory symptoms in patients with drug-naive restless legs syndrome. Sleep Med 2013;14:1369–74.
[27] Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996;47:1435–41.
[28] Shukla G, Gupta A, Pandey RM, et al. What features differentiate unilateral from bilateral restless legs syndrome? A comparative observational study of 195 patients. Sleep Med 2014;15:714–9.
[29] Karroum EG, Leu-Semenescu S, Arnulf I. Topography of the sensations in primary restless legs syndrome. J Neurol Sci 2012;320:26–31.
[30] Goulart LI, Delgado Rodrigues RN, Prieto Peres MF. Restless legs syndrome and pain disorders: what's in common? Curr Pain Headache Rep 2014;18:461.
[31] Winkelman JW, Gagnon A, Clair AG. Sensory symptoms in restless legs syndrome: the enigma of pain. Sleep Med 2013;14:934–42.
[32] Trenkwalder C, Zieglgansberger W, Ahmedzai SH, et al. Pain, opioids, and sleep: implications for restless legs syndrome treatment. Sleep Med 2017;31:78–85.
[33] Karroum EG, Golmard JL, Leu-Semenescu S, et al. Sensations in restless legs syndrome. Sleep Med 2012;13:402–8.
[34] Winkelmann J, Wetter TC, Collado-Seidel V, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 2002;23:597–602.
[35] Bassetti CL, Mauerhofer D, Gugger M, et al. Restless legs syndrome: a clinical study of 55 patients. Eur Neurol 2001;45:67–74.
[36] Karroum EG, Golmard JL, Leu-Semenescu S, et al. Painful restless legs syndrome: a severe, burning form of the disease. Clin J Pain 2015;31:459–66.
[37] Stiasny-Kolster K, Pfau DB, Oertel WH, et al. Hyperalgesia and functional sensory loss in restless legs syndrome. Pain 2013;154:1457–63.
[38] Bachmann CG, Rolke R, Scheidt U, et al. Thermal hypoaesthesia differentiates secondary restless legs syndrome associated with small fibre neuropathy from primary restless legs syndrome. Brain 2010;133:762–70.
[39] Stiasny-Kolster K, Magerl W, Oertel WH, et al. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. Brain 2004;127:773–82.
[40] Polydefkis M, Allen RP, Hauer P, et al. Subclinical sensory neuropathy in late-onset restless legs syndrome. Neurology 2000;55:1115–21.
[41] Bastia JK, Bhoi SK, Kalita J, et al. Neuropathy in a cohort of restless leg syndrome patients. J Clin Neurosci 2015;22:1314–8.
[42] Kerr S, McKinon W, Bentley A. Descriptors of restless legs syndrome sensations. Sleep Med 2012;13:409–13.
[43] Wandner LD, Scipio CD, Hirsh AT, et al. The perception of pain in others: How gender, race, and age influence pain expectations. J Pain 2012;13:220–7.
[44] Ondo WG. Movements mimicking myoclonus associated with spinal cord pathology: is this a “pure motor restless legs syndrome”? Tremor Other Hyperkinetic Mov 2012:2.
[45] Akpnar U, Yardm M, Akyatan N. Familial and single cases of restless leg syndrome. Gülhane Tıp Derg. 2011;53:77–84.
[46] Gemignani F, Marbini A, Di Giovanni G, et al. Cryoglobulinaemic neuropathy manifesting with restless legs syndrome. J Neurol Sci 1997;152:218–23.

[47] Ingram DG, Plante DT. Seasonal trends in restless legs symptomatology: evidence from Internet search query data. Sleep Med 2013;14:1364–8.
[48] Ekbom KA. Chapter 7: case reports, vol. 121; 1945. p. 74–118.
[49] Zhu XY, Liu Y, Zhang XJ, et al. Clinical characteristics of leg restlessness in Parkinson's disease compared with idiopathic restless legs syndrome. J Neurol Sci 2015;357:109–14.
[50] Koo BB. Restless legs syndrome: relationship between prevalence and latitude. Sleep Breath 2012;16:1237–45.
[51] Dubocovich ML. Melatonin is a potent modulator of dopamine release in the retina. Nature 1983;306:782–6.
[52] Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61:304–9.
[53] Allen RP, Earley CJ. The role of iron in restless legs syndrome. Move Disord 2007;22(18):S440–8.
[54] Curgunlu A, Doventas A, Karadeniz D, et al. Prevalence and characteristics of restless legs syndrome (RLS) in the elderly and the relation of serum ferritin levels with disease severity: hospital-based study from Istanbul, Turkey. Arch Gerontol Geriatr 2012;55:73–6.
[55] Frauscher B, Gschliesser V, Brandauer E, et al. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Med 2009;10:611–5.
[56] Maes M, Bosmans E, Scharpe S, et al. Components of biological variation in serum soluble transferrin receptor: relationships to serum iron, transferrin and ferritin concentrations, and immune and haematological variables. Scand J Clin Lab Investig 1997;57:31–41.
[57] Trenkwalder C, Allen R, Hogl B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol 2018;17:994–1005.
[58] Khan FH, Ahlberg CD, Chow CA, et al. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. J Neurol 2017;264:1634–41.
[59] Rye DB. The molecular genetics of restless legs syndrome. Sleep Med Clin 2015;10:227–33 [xii].
[60] Earley CJ, Connor J, Garcia-Borreguero D, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom Disease). Sleep Med 2014;15:1288–301.
[61] Davis BJ, Rajput A, Rajput ML, et al. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. Eur Neurol 2000;43:70–5.
[62] Wang J, O'Reilly B, Venkataraman R, et al. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: a randomized, double-blind, placebo-controlled study. Sleep Med 2009;10:973–5.
[63] Lammers N, Curry-Hyde A, Smith AJ, et al. Are serum ferritin and transferrin saturation risk markers for restless legs syndrome in young adults? Longitudinal and cross-sectional data from the Western Australian Pregnancy Cohort (Raine) Study. J Sleep Res 2018:e12741.
[64] Earley CJ, Connor JR, Beard JL, et al. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000;54:1698–700.
[65] Cho YW, Kim KT, Lee YS, et al. White matter hyperintensities on brain magnetic resonance imaging: comparison of early-onset and late-onset restless legs syndrome. Sleep Med 2016;25:4–7.
[66] Rinaldi F, Galbiati A, Marelli S, et al. Defining the phenotype of restless legs syndrome/Willis-Ekbom disease (RLS/WED): a clinical and polysomnographic study. J Neurol 2016;263:396–402.
[67] Moon HJ, Chang Y, Lee YS, et al. T2 relaxometry using 3.0-Tesla magnetic resonance imaging of the brain in early- and late-onset restless legs syndrome. J Clin Neurol 2014;10:197–202.
[68] Margariti PN, Astrakas LG, Tsouli SG, et al. Investigation of unmedicated early onset restless legs syndrome by voxel-based morphometry, T2 relaxometry, and functional MR imaging during the night-time hours. AJNR Am J Neuroradiol 2012;33:667–72.